

Detection of coronary artery disease by thallium scintigraphy in patients with valvar heart disease

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SUMMARY In patients with valvar heart disease detection of coronary artery disease by conventional non-invasive methods may be difficult. The usefulness of thallium-201 exercise scintigraphy for detecting coronary artery disease was evaluated in 16 patients with aortic stenosis, 17 with aortic regurgitation, nine with mitral stenosis, and six with mitral regurgitation who were investigated by coronary angiography. Only two of 21 patients with $\geq 50\%$ coronary artery obstruction had normal thallium images. Three patients without angiographic evidence of coronary artery stenoses had perfusion defects demonstrated by thallium scintigraphy. Only one patient with $\geq 75\%$ coronary stenosis had a normal thallium scan. Angina pectoris or ST segment depression evoked by exercise test were not useful in distinguishing patients with coronary artery disease from those with normal coronary vessels.

These data suggest that thallium exercise scintigraphy may be a useful non-invasive test for detecting coronary artery disease in patients with valvar heart disease.

In patients with valvar heart disease diagnosis of coronary artery disease is difficult without coronary arteriography.¹⁻³ Angina pectoris is an unreliable marker of coronary heart disease, and its absence does not exclude coronary artery disease.¹⁻³ Even exercise electrocardiography does not reliably detect anatomical coronary lesions in patients with valvar heart disease.⁴⁻⁶

Thallium scintigraphy is a sensitive and specific method for detecting angiographically important coronary artery disease,^{6,7} but there is little information on its value in patients with valve diseases.⁸⁻¹⁰ We have assessed the usefulness of thallium scintigraphy in patients with either aortic or mitral valve disease.

Patients and methods

Patients

Forty eight consecutive patients (26 women and 22

men, mean (SD) age 55 (10) years) referred for invasive evaluation of valvar heart disease were studied by thallium exercise scintigraphy and coronary angiography. Beta blocking agents were withdrawn gradually at least 48 hours before the studies. Invasive studies showed aortic stenosis in 16 patients, aortic regurgitation in 17, mitral stenosis in nine, and mitral regurgitation in six. Fifteen patients with aortic valve disease had combined aortic stenosis and regurgitation, and 10 had combined mitral stenosis and regurgitation. Three patients had combined aortic and mitral valve disease. Four patients had mild valvar disease (two with aortic stenosis, one with aortic regurgitation, and one with mitral stenosis), while the others had moderate to severe valve lesions (aortic valve area $< 1.2 \text{ cm}^2$, mitral valve area $< 1.5 \text{ cm}^2$, and 3-4/4 valvar regurgitation in aortography or left ventricular cineangiography). Patients with a history of previous myocardial infarction (two patients) or exertional syncope, inability to perform bicycle ergometer exercise, or congestive heart failure were excluded from the consecutive series. Informed consent was obtained from all the patients.

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CARDIAC CATHETERISATION

All patients underwent left sided cardiac catheterisation, including selective coronary arteriography performed by the Judkins technique. Patients with suspected mitral valve disease also underwent right sided catheterisation. High flow coronary catheters were used in most patients with aortic disease in order to obtain adequate opacification of the coronary arteries. Left ventricular cineangiograms were performed as described elsewhere.¹¹ Cardiac output was determined by the Fick method, and the valve areas were calculated by a modification of Gorlin's formula.¹² The presence and severity of aortic regurgitation were evaluated by aortic root angiography. The angiographic findings were interpreted by two observers who were unaware of the scintigraphic studies. Reduction of $\geq 50\%$ in the luminal diameter of a coronary artery was regarded as an important lesion.

EXERCISE ELECTROCARDIOGRAPHY

A symptom limited exercise test on an electrically braked bicycle ergometer was performed two days before the catheterisation studies. The exercise was started at 30 W and the workload was increased in one minute steps by 15 W for men and 10 W for women. The final workload was the individual maximum determined by the symptoms of angina, dyspnoea, or fatigue. Standard electrocardiographic leads I, aVF, and V5 were monitored.¹³ Cuff blood pressure, heart rate, and ST segment depression were determined every minute up to five minutes after exercise. The electrocardiogram was considered to be positive if more than 0.1 mV ST segment depression was noted during or after the exercise test.

THALLIUM-201 SCINTIGRAPHY

Thallium scintigraphy studies were performed on the day preceding catheterisation by the same exercise protocol that was used for exercise electrocardiography. Thallium-201 (2 mCi (74 MBq)) was injected intravenously 30 to 60 s before completion of the ergometric exercise. Four minutes after the injection imaging was started in the anterior and 45° and 70° left anterior oblique positions with a Siemens Rota-75 gamma camera with a low energy high sensitivity collimator. Post-exercise imaging was completed within 30 min. Scintigraphic imaging was repeated in the same projections four hours after exercise.

Scintigraphic data were collected on a 64 × 64 byte matrix in multigated form for five minutes for each of the views. The images were stored on a Gamma-11 computer disc for analysis. The computer images were enlarged, interpolated, and subjected to back-

ground subtraction.¹⁴ Computer-generated circumferential profiles were obtained from the exercise and delayed images as follows. The myocardium was divided into 36 sectors and radii extending from its centre to its outside contour were constructed by computer. The division into sectors started at 12 o'clock and moved clockwise. The following circumferential curves were calculated from the background subtracted, smoothed images: (a) number of pixels/sector and (b) the normalised counts/pixel. The same regions of interest were used for the post-exercise and delayed images. These curves were displayed on the same image as the normal curves (2 SD) obtained previously.

The scintigrams were interpreted independently by two observers who were not aware of the angiographic findings. Three segments in each view were analysed (anterior, apical, and inferior segment in the anterior projection; posterior, apical, and septal in the 45° left anterior oblique projection; and inferior, apical, and anterior in the 70° left anterior oblique projection). The scintigram was interpreted as indicating coronary artery disease if any area of decreased post-exercise perfusion with or without redistribution in the delayed images was present. An apical defect alone was not considered abnormal, however. Observer agreement was complete in 94% of images. In the remaining 6% (four cases) a consensus was reached with the aid of a third independent observer.

Sensitivity was defined as the number of true positives multiplied by 100 divided by the sum of true positives plus false negatives, specificity as the number of true negatives multiplied by 100 divided by the sum of true negatives plus false positives, and negative predictive accuracy as the number of true negatives multiplied by 100 divided by true negatives plus false negatives.

Results

CLINICAL DATA

Table 1 shows the clinical and exercise data. All the patients had symptoms related to heart disease. Twenty eight had angina pectoris. The sensitivity of angina in predicting the presence of coronary artery disease was 67% (86% for aortic stenosis, 83% for aortic regurgitation, 30% for mitral stenosis, and 100% for mitral regurgitation), and its specificity was 59% (44% for aortic stenosis, 64% for aortic regurgitation, 100% for mitral stenosis, and 60% for mitral regurgitation). The sensitivity of exercise electrocardiography in detecting coronary artery disease was 81% and its specificity was only 52%.

Table 1 Clinical and exercise data (mean (SD))

	Aortic stenosis (n = 16)	Aortic regurgitation (n = 17)	Mitral stenosis (n = 9)	Mitral regurgitation (n = 6)
Age (years)	56 (11)	51 (9)	61 (6)	55 (5)
Sex (males/females)	12/4	8/9	1/8	3/3
New York Heart Association class:				
I or II	4 (25%)	7 (41%)	2 (22%)	3 (50%)
III or IV	12 (75%)	10 (59%)	7 (78%)	3 (50%)
Severity of valve lesion:				
2/4	2 (12%)	1 (6%)	1 (11%)	0
3/4	11 (69%)	11 (65%)	7 (78%)	4 (67%)
4/4	3 (19%)	5 (29%)	1 (11%)	2 (33%)
Occurrence of angina pectoris	12 (75%)	9 (53%)	3 (33%)	2 (33%)
Coronary artery obstructions:				
None	9 (56%)	11 (64%)	2 (22%)	5 (63%)
1 vessel disease	4 (25%)	2 (12%)	2 (22%)	1 (17%)
2 vessel disease	1 (6%)	2 (12%)	3 (34%)	0
3 vessel disease	2 (13%)	2 (12%)	2 (22%)	0
Ergometer exercise data:				
Heart rate _{max} (beats/min)	112 (21)	122 (19)	127 (30)	130 (25)
ST-segment depression	10 (63%)	9 (53%)	5 (56%)	5 (83%)

RELATION BETWEEN SCINTIGRAPHIC DATA AND CORONARY ANGIOGRAPHY

Table 2 shows the occurrence of thallium defects and the presence of angiographically important coronary artery disease in the various groups. Two aortic stenosis patients with angiographically important coronary artery lesions (one with 75% stenosis of the right coronary artery, and the other with 50% stenosis of the left anterior descending coronary artery) had normal scintigraphic images. During exercise neither of these patients reached a heart rate of more than 60% of the age-predicted maximum. Two patients with aortic regurgitation and one with mitral stenosis had abnormal scintigraphy (two patients had fixed anterior defects and one patient had a reversible inferior defect) despite the absence of angiographically important coronary lesions.

When coronary artery stenosis of $\geq 75\%$ was used as the cut-off point, 17 patients had coronary artery disease and only one of these had a normal thallium scan (sensitivity 94%, specificity 90%, and negative

predictive accuracy 97%). Figures 1 and 2 show a true positive scan and a true negative scan. Some of the patients with aortic valve disease had apical perfusion defects, which were not considered to be abnormal.

Discussion

Thallium scintigraphy is a valuable non-invasive method for detecting coronary artery disease,^{6,7} but its usefulness in patients with valvular heart disease has been little studied. Routine cardiac catheterisation could be avoided in some patients with valve disease¹⁵ if coronary artery disease could be assessed non-invasively before valve surgery, and where necessary coronary artery bypass grafting could continue to be done at the same time as valve operation. Our thallium imaging data proved to be reasonably reliable in detecting coronary artery disease in patients with valve lesions; their sensitivity and specificity resembled values obtained in patients without valve lesions.⁶

Table 2 Relation of thallium scintigraphy to presence and absence of coronary artery disease

Coronary artery disease	Number of patients	Normal thallium-201 scintigraphy	One or more thallium-201 defects
Present:			
Aortic stenosis	7	2	5
Aortic regurgitation	6	0	6
Mitral stenosis	7	0	7
Mitral regurgitation	1	0	1
Absent:			
Aortic stenosis	9	9	0
Aortic regurgitation	11	9	2
Mitral stenosis	2	1	1
Mitral regurgitation	5	5	0

Overall sensitivity of thallium scintigraphy, 90%; and specificity, 89%.

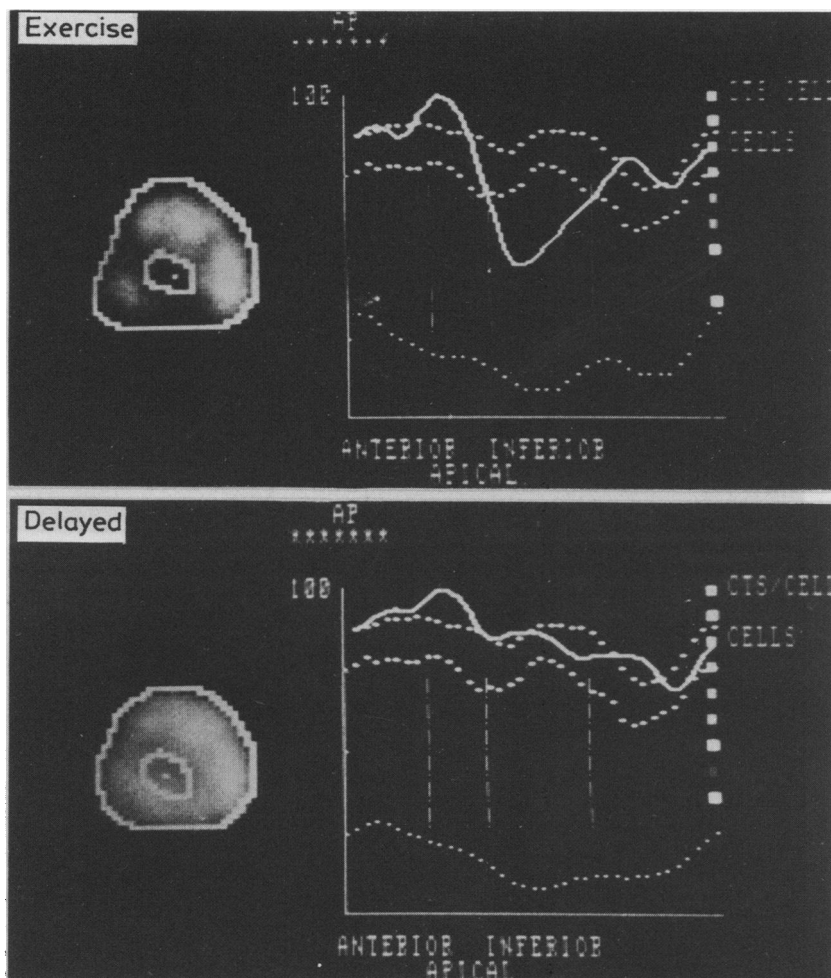


Fig. 1 A thallium scan of a patient with aortic stenosis and stenosis of left anterior descending coronary artery (50%) and right coronary artery (90%). A smoothed, background subtracted, and contrast enhanced thallium image on the left and the corresponding circumferential profile curve on the right (a solid line) show moderately decreased thallium activity of inferoapical segment and a small thallium defect in the anterior segment on the post-exercise image (upper). There is complete redistribution of initial defects on the delayed images (lower). The uppermost dotted line in the profile curve represents normal thallium activity curve, the middle -2 SD from normal, and the lowest dotted line represents the thickness of a left ventricle wall in pixels (CELLS). Counts/pixel (CTS/CELL) in circumferential profile curve are normalised to 100% (solid line). AP, anteroposterior view.

Imaging studies in patients with aortic valve disease have produced conflicting results.^{8,9} Bailey *et al* concluded that qualitative thallium imaging does not allow adequate separation of patients with aortic stenosis and coronary artery disease from those with normal coronary angiography,⁸ whereas, like us,

Pfisterer *et al* found that thallium scintigraphy is reliable for cases of aortic valve disease, provided that apical perfusion defects are not considered to represent coronary artery disease.⁹ Although isotope imaging has been studied in cases of mitral valve prolapse,¹⁵ its usefulness in patients with mitral

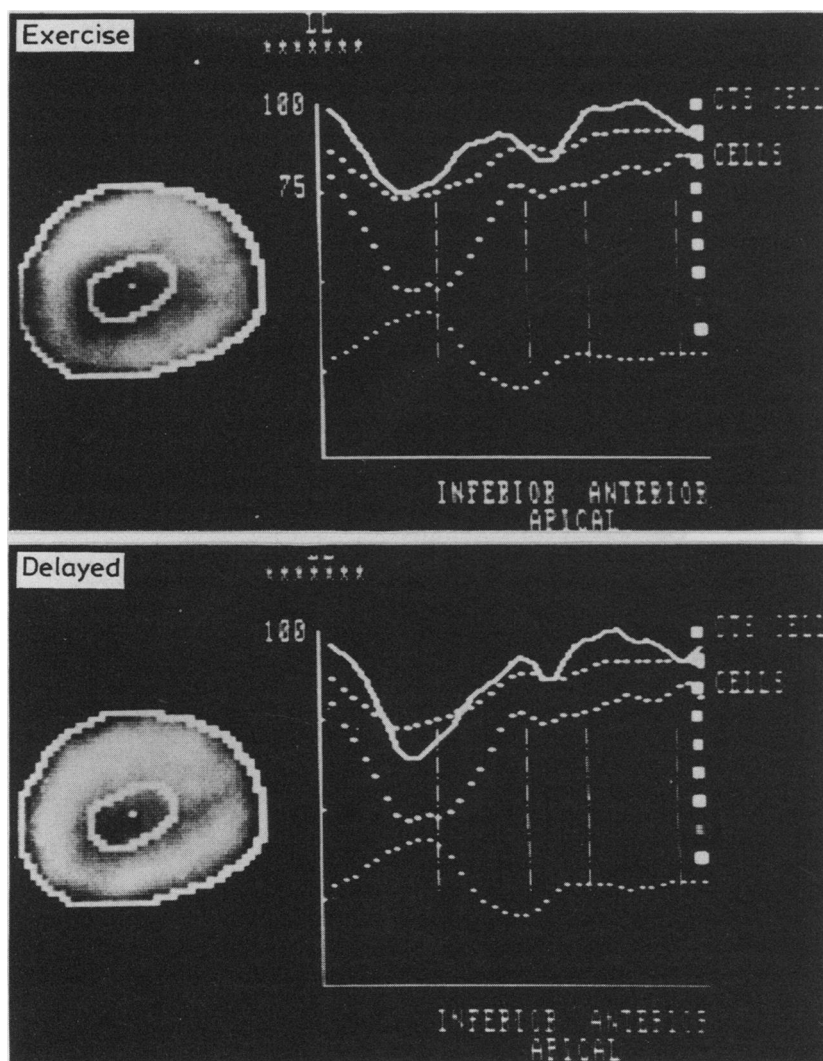


Fig. 2 A thallium scan of a patient with aortic regurgitation and normal coronary angiography. The scintigraphy shows normal thallium activity despite a very slight thinning of apical segment, which was not regarded as abnormal. The uppermost dotted line in the profile curve represents normal thallium activity curve, the middle -2 SD from normal, and the lowest dotted line represents the thickness of a left ventricle wall in pixels (CELLS). Counts/pixel (CTS/CELL) in circumferential profile curve are normalised to 100% (solid lines). LL, left lateral view.

stenosis or regurgitation has not so far been thoroughly examined. Our preliminary data in a small group of patients showed that thallium imaging was quite sensitive and specific in such patients.

Two patients with aortic stenosis had normal thallium scans despite angiographic evidence of coro-

nary artery disease. Both of these patients had low exercise tolerance and they did not reach the acceptable heart rate during exercise. In such cases pharmacological stress testing with dipyridamole might increase the sensitivity of the imaging.¹⁶ As shown by others⁹ apical perfusion defects were quite com-

mon in patients with aortic valve lesions. Apical defects are believed to be a result of alterations in left ventricular geometry without a change in radio-nuclide perfusion.¹⁷

Only one of our patients with $\geq 75\%$ coronary stenosis had a normal thallium scan. Thus in this series thallium imaging was 97% accurate in excluding severe coronary artery disease. The number of patients we studied was small, however, and they do not establish that coronary angiography can be replaced by thallium scintigraphy in patients with valve lesions. Larger studies would allow the analysis of patients by subset (that is type of valve lesion, age, sex, and coronary risk factors), and they should show whether important coronary artery disease can be excluded by non-invasive examination in patients with valvar heart disease.

References

- 1 Coleman EH, Soloff LA. Incidence of significant coronary artery disease in rheumatic valvular heart disease. *Am J Cardiol* 1976;25:401-4.
- 2 Ramsdale DR, Bennett DH, Bray CL, Ward C, Beton DC, Faragher EB. Angina, coronary risk factors and coronary artery disease in patients with valvular disease. A prospective study. *Eur Heart J* 1984; 5:716-26.
- 3 Mandal AB, Gray IR. Significance of angina pectoris in aortic valve stenosis. *Br Heart J* 1976;38:811-5.
- 4 Harris CN, Aronow WS, Parker DP, Kaplan MA. Treadmill stress test in left ventricular hypertrophy. *Chest* 1973;63:353-7.
- 5 Aronow WS, Harris CN. Treadmill exercise test in aortic stenosis and mitral stenosis. *Chest* 1975;68:507-9.
- 6 Gibson RS, Beller GA. Should exercise ECG testing be replaced by radioisotope methods? In: Breast A, ed. *Controversies in cardiology. Cardiovascular clinics*. Philadelphia: FA Davis, 1982:1-31.
- 7 Iskandrian AS, Hakki AH. Thallium-201 myocardial scintigraphy. *Am Heart J* 1985;109:113-29.
- 8 Bailey IK, Come PC, Kelly DT, et al. Thallium-201 myocardial perfusion imaging in aortic valve stenosis. *Am J Cardiol* 1977;40:889-99.
- 9 Pfisterer M, Muller-Braud J, Brundler H, Cueni T. Prevalence and significance of reversible radio-nuclide ischemic perfusion defects in symptomatic aortic valve disease patients with or without concomitant coronary disease. *Am Heart J* 1982;103:92-6.
- 10 Klein GJ, Kostuk WJ, Boughner DR, Chamberlain MJ. Stress myocardial imaging in mitral leaflet prolapse syndrome. *Am J Cardiol* 1978;42:746-50.
- 11 Huikuri HV, Ikäheimo MJ, Linnaluoto MMK, Takkinen JT. Left ventricular response to isometric exercise and its value in predicting the change in ventricular function after mitral valve replacement for mitral regurgitation. *Am J Cardiol* 1983;51:1110-5.
- 12 Hammermeister KE, Murray JA, Blackmon JR. Revision of Gorlin constant for calculation of mitral valve area from left heart pressures. *Br Heart J* 1973;35:392-6.
- 13 Rajasalmi M, Takkinen JT. Exercise tests, atrial pacing and myocardial lactate extraction in relation to coronary arteriography in young patients with angina pectoris. *Am Heart J* 1978;40:712-8.
- 14 Goris ML, Daspit SG, McLaughlin P, Kriss JP. Interpolative background subtraction. *J Nucl Med* 1976;17:744-7.
- 15 Brandenburg RO. No more routine catheterization for valvular heart disease? *N Engl J Med* 1981; 305:1277-8.
- 16 Leppo J, Boucher CA, Okada RD, Novell JB, Strauss HW, Pohost GM. Serial thallium-201 myocardial imaging after dipyridamole infusion: diagnostic utility in detecting coronary stenoses and relationship to regional wall motion. *Circulation* 1982;66:649-57.
- 17 Gerwitz H, Gritte GJ, Strauss HW, et al. The influence of left ventricular volume and wall motion on myocardial images. *Circulation* 1979;59:1172-7.